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CONTRACTING ORGANIZATION: Stanford University School of Medicine

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14. ABSTRACT Omalizumab is currently the only FDA approved monoclonal anti-IgE therapy. We solved the IgE:omalizumab crystal structure to 2.54 Å. This structure elucidates the mechanism of omalizumab inhibition of IgE:FcεRIα and IgE:CD23 interactions, and explains omalizumab's selectivity for free circulating IgE. Surprisingly, the complex structure shares significant similarity with the disruptive IgE inhibitor E2_79, and provides mechanistic insight into the efficiency with which disruptive inhibitors are able to bind to, and accelerate FcεRIα dissociation from preformed IgE:FcεRIα complexes. Structural information from the IgE:omalizumab complex was used to generate a point mutation in the IgE-Fc, yielding an omalizumab-resistant IgE. Omalizumab-resistant IgE, in combination with omalizumab, promotes the exchange of the IgE repertoire on human basophils. This combination treatment demonstrates the possibility of substituting rather than depleting the IgE repertoire, thereby exchanging harmful, allergen-specific IgE while maintaining endogenous IgE-dependent regulatory mechanisms that may further suppress the allergic response.					
15. SUBJECT TERMS Allergy, IgE, anti-IgE therapy, IgE repertoire exchange					
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1. INTRODUCTION:

IgE antibodies bind the high affinity IgE Fc receptor (FcεRI), found primarily on mast cells and basophils, and trigger inflammatory cascades of the allergic response. Inhibitors of IgE:FcεRI binding have been identified and an anti-IgE therapeutic antibody (omalizumab) is used to treat severe allergic asthma and is being used experimentally for the treatment of food allergies. However, improved therapeutics are needed for the treatment of allergies. We are taking a two-pronged approach to developing improved therapeutics. The first approach is based on our observations that a novel class of anti-IgE inhibitors (DARPin), which can actively take apart receptor complexes, exhibits improved therapeutic potency in a mouse passive cutaneous anaphylaxis model. We propose to develop novel antibody therapeutics with this disruptive activity using a systematic set of experiments. In our second approach, we are pursuing the identification of small molecule inhibitors of the IgE:receptor interaction, since this would potentially allow for the treatment of a broader patient population. We have developed and implemented novel assay tools and approaches to enable the discovery of small molecule inhibitors. We feel that both approaches have significant and complementary value and we have made good progress in our research in both areas during the past year.

2. KEYWORDS:

Allergy, IgE antibodies, high affinity IgE receptor, FcεRI, accelerated dissociation, high throughput screening

3. ACCOMPLISHMENTS:

Major goals and accomplishments

Overview of proposed task and current accomplishments		
Specific Aim 1: Development of a novel anti-IgE antibody with potent disruptive inhibitor activity	Proposed timeframes	Current Status (12 months)
Major Task 1: Generate and characterize novel bifunctional anti-IgE antibodies		
Subtask 1: Bispecific antibody protein expression and purification	1-12	In progress
Subtask 2: Bispecific antibody protein functional studies	12-24	Not yet started
Subtask 3: Isolation of antibodies using phage display	1-12	Completed
Subtask 5: Functional studies with phage-derived Fabs	12-24	In progress
Subtask 6: Production and characterization of bifunctional antibodies using phage-derived Fab	12-36	Not yet started
Subtask 7: Elicitation of site specific antibodies from boost-prime immunization	12-36	Not yet started
Subtask 4: Structural studies of Fab:IgE complexes	6-36	Completed structure of IgE-Fc:omalizumab complexes, crystallized ligelizumab:IgE

		complexes
Specific Aim 1 Milestones:		
Milestone 1 Year 1: Express, purify and characterize chimeric omalizumab constructs	Month 10	Completed first set of constructs; designing new constructs, developing new antibodies
Milestone 2 Year 1: Conduct phage display experiments with wt and mutant IgE-Fc	Month 10	Obtained yeast display library, generated selection reagents (IgE), completed anti-IgE selection experiments
Milestone 3 Year 2: Analyze and optimize bispecific omalizumab and phage display anti-IgE constructs	Month 8	Expressed a subset of novel anti-IgE antibodies, analyzed disruptive activity, initiated additional rounds of
Milestone 4 Year 3: Complete structural analysis of anti-IgE complexes	Month 8	Completed structure of omalizumab:IgE complex; obtained preliminary crystals of ligelizumab:IgE-Fc crystals screening for additional complex crystals
Milestone 5 Year 3: Analyze anti-IgE immunization response, optimize best chimeric anti-IgE construct	Month 10	Not yet started
Specific Aim 2: Identification and validation of candidate small molecule IgE inhibitors from high throughput screening.		
Major Task 2: Structure-function studies of small molecule lead compounds		
Subtask 1: Dose response screening of top (380) compounds from high throughput screening	1-8	Completed
Subtask 2: Functional studies of lead compounds using ELISA, cell-based and Biacore assays	6-24	Completed functional analysis of lead compounds from HTS
Subtask 3: Binding and inhibition studies with analogs of candidate lead inhibitors	18-36	In progress
Subtask 4: Crystal structure analysis of lead compounds with IgE or receptor proteins	6-36	In progress
Specific Aim 2 Milestones:		
Milestone 1 Year 1: Complete biochemical and cell-based inhibition studies with lead compounds from screening	Month 6	Completed
Milestone 2	Month 8	Completed

Year 1: Complete direct SPR binding studies with lead compounds from screening		
<p>Milestone 3</p> <p>Year 2: Study top compound analogs in biochemical, cell-based and SPR binding assays.</p>	Month 8	<p>HTS lead analogs identified and studied. Established collaboration with chemist to initiated SPR-based fragment screening to identify additional lead compounds</p> <p>Obtained additional libraries for screening</p>
<p>Milestone 4</p> <p>Year 3: Complete structural analyses of lead compounds and analogs</p>	Month 8	In progress – soaked crystals with compounds; pursuing co-crystallization studies

During the past year we have continued making progress on both aims of this project. We completed the structure determination of the omalizumab:IgE complex, which was published in *Nature Communications*, and pursued our major goals as described in detail below.

Specific Aim 1: Development of a novel anti-IgE antibody with potent disruptive inhibitor activity

Major Task 1: Generate and characterize novel bifunctional anti-IgE antibodies

Year 1 & 2 milestones

- Express, purify and characterize chimeric omalizumab constructs*
- Conduct phage display experiments with wt and mutant IgE-Fc*
- Analyze and optimize bispecific omalizumab and phage display anti-IgE constructs*

During the past year, we invested a significant effort in developing the yeast display system in the laboratory for the selection of novel anti-IgE antibodies and for developing approaches to identifying disruptive antibody-based inhibitors. This has involved research in two directions. First, we have engineered yeast with our known anti-IgE molecules, so that these can provide a set of reference strains representing different functional characteristics. We have engineered yeast strains for surface display of E2_79, E3_53 and a single chain variant of omalizumab (Fig. 1). All of the proteins are expressed well on the surface of yeast and bind IgE, as monitored by flow cytometry with biotinylated IgE-Fc.

We have used these engineered yeast to devise an approach

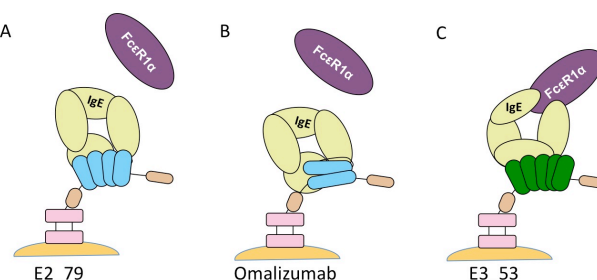


Fig. 1. Schematics of yeast surface display constructs for E2_79, omalizumab scFv and E3_53.

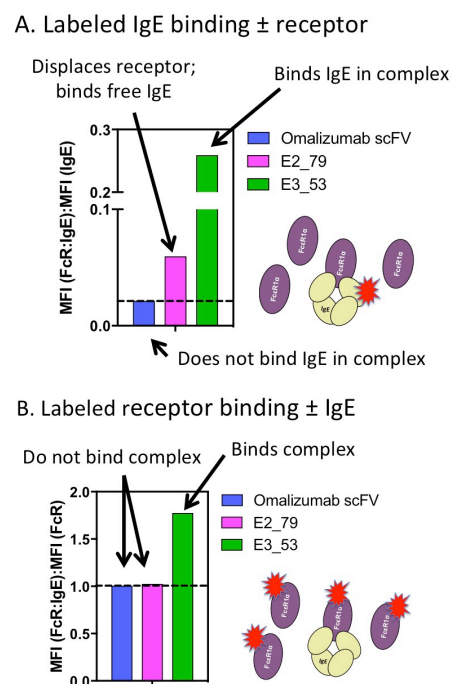


Figure 2. Profiles of anti-IgE ligands displayed on yeast surface. Ratios of the mean fluorescence intensities (MFIs) of yeast stained with labeled IgE (A) or labeled Fc ϵ RI (B) in preformed complexes or alone.

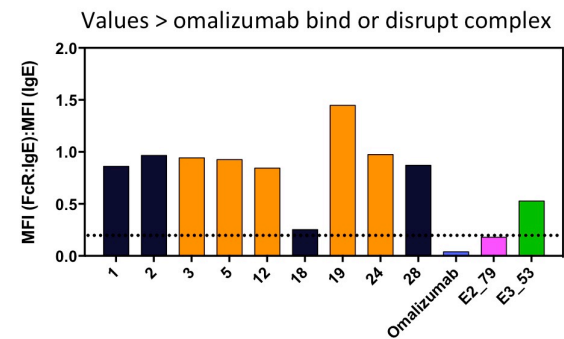
to distinguish disruptive IgE inhibitors (E2_79), non-competitive IgE binders (E3_53) and standard competitive inhibitors (omalizumab scFv). First, yeast are stained with labeled IgE alone and separately in a preformed complex with FcεRI. The ratio of bound IgE ± FcεRI indicates whether the yeast ligand competes with receptor (Fig. 2A). Omalizumab shows very little binding to IgE:FcεRI complexes, while the non-competitive E3_53 readily binds labeled IgE associated with FcεRI (Fig. 2A). E2_79 shows greater binding to IgE presented as complex compared to omalizumab, but lower binding than E3_53, consistent with its ability to accelerate dissociation of the preformed complexes.

To further distinguish between non-competitive ligands and potentially disruptive inhibitors, we also stain the yeast with labeled FcεRI in the presence and absence of unlabeled IgE. In these experiments, non-competitive ligands like E3_53 should bind more labeled FcεRI in the presence of IgE over the background FcεRI (Fig. 2B). Competitive and disruptive inhibitors, like omalizumab and E2_79, exhibit no binding of labeled FcεRI in IgE complexes as compared to the background FcεRI staining (Fig. 2B). These assays clearly discriminate between our known IgE ligands, providing template profiles for selecting improved disruptive inhibitors using yeast surface display libraries.

We have been pursuing the identification of novel anti-IgE antibodies using a yeast display human scFv library obtained from the Wittrup lab at MIT. We initially screened for clones that bind both IgE-Fc and intact IgE with estimated affinities of 50-100 nM. After multiple rounds of magnetic bead selection, we isolated clones by FACS and identified 21 unique anti-IgE clones by sequencing. Although the clones represent a diversity of sequences, 6 share a common VH region, suggesting these bind the same IgE region.

We have initially selected 9 clones that showed the highest IgE binding levels for further analysis. The ability of the scFvs to bind labeled IgE in the presence or absence of receptor (Fig. 3A) showed that most bound similar amounts of IgE regardless of whether the IgE was free or in a complex. Clone 18 exhibited a profile very similar to E2_79, being better than omalizumab, but not as good as E3_53. The other scFv clones bind the complexed IgE even better than E3_53. Staining of the yeast with labeled FcεRI in the presence and absence of IgE-Fc was also revealing (Fig. 3B). All of the scFv yeast, along with E2_79 and omalizumab, show no binding of FcεRI in complex over the background, contrasting with the non-competitive E3_53 control. These observations indicate that the scFvs compete for receptor binding to IgE. These are very exciting results that demonstrate that we can isolate

A. Ratio of labeled IgE binding ± unlabeled FcεRI



B. Ratio of labeled FcεRI binding ± unlabeled IgE

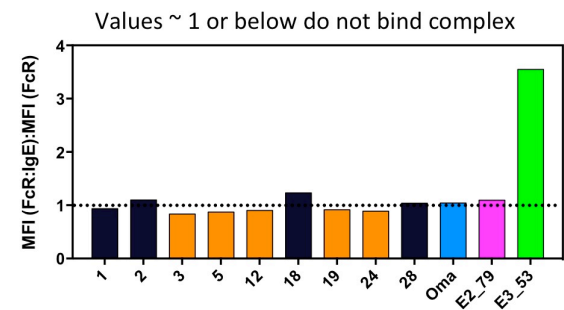


Figure 3. Screening anti-IgE clones for disruptive inhibition. (A) Ratio of staining yeast cells with labeled IgE prebound to FcεRI compared to labeled IgE alone. (B) Ratio of staining yeast cells with labeled FcεRI prebound to IgE compared to labeled FcεRI alone. Individual clones are stained separately in parallel experiments with the reagents, the mean fluorescence intensity measure by flow cytometry and the ratio calculated. Numbers represent individual IgE-binding scFv yeast clones isolated by multiple rounds of selection. Orange bars represent clones with a shared VH segment (but differing VL). Omalizumab, E2_79 and E3_53 controls are run in parallel to the yeast samples. ScFv clone 18 shows behavior very similar to E2_79. Other scFv clones bind IgE in receptor complexes better and do not pull down labeled receptor bound to IgE, suggesting that these are also competitive and potentially disruptive inhibitors.

novel anti-IgE antibodies with characteristics of disruptive inhibitors. It will be very interesting to follow up on these

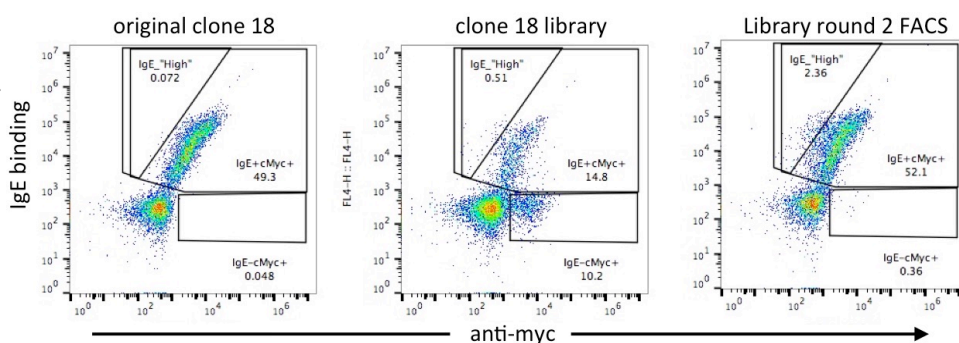


Figure 4. Yeast surface display and selection of mutated anti-IgE scFv clone 18 from an error-prone PCR library.

We are very interested in the activity of clone 18, given its similar activity profile to E2_79. However, initial attempts at expressing this clone in mammalian cells suggested that it may be somewhat unstable and express poorly. We were therefore interested in selecting variants of clone 18 with improved expression, stability and affinity for IgE. We generated a randomly mutated library for the selection of stabilized clone 18 variants using the GeneMorph II kit, with a mutation rate of ~ 5 base changes per gene. We were seeking to generate a library with $\sim 10^8$ mutants. The initial library showed reduced binding to IgE relative to the original clone 18 (Figure 4). However, after rounds of magnetic bead and FACS selection, we observed a clear enrichment of IgE binding as well as a population of “IgE high” clones. We are in the process of sequencing the resulting clones and analyzing these data further. However, these data demonstrate that we can produce and select scFv variants from libraries produced in the laboratory. This opens the opportunity for selecting scFvs and scFv variants that may show improved disruptive inhibitor activity. Analysis of our other novel anti-IgE clones is ongoing.

Specific Aim 2: Identification and validation of candidate small molecule IgE inhibitors from high throughput screening.

Major Task 2: Structure-function studies of small molecule lead compounds

Year 1 & 2 milestones

- Complete biochemical and cell-based inhibition studies with lead compounds from screening*
- Complete direct SPR binding studies with lead compounds from screening*
- Study top compound analogs in biochemical, cell-based and SPR binding assays.*

During the past year we have been focusing on studies of our three lead compounds, identified from a prior HTS screen and we have also broadened our approach by initiating screens with two fragment libraries available to us at Stanford. These studies have focused on measuring direct binding interactions between the small molecules and IgE and on obtaining structural validation of their binding by X-ray crystallography. In addition, we have initiated three new collaborations with chemistry laboratories. With the Scheuerman group at the ETH Zurich, we have conducted a screen with a novel Dual-Display DNA-encoded fragment library. The analysis of the screening results is currently in progress. We have initiated a collaboration with the Domling laboratory at the University of Groningen, to screen and synthesize novel cyclic peptides as an alternative route to IgE inhibitors. Finally, we have established a collaboration with Nicolai Cramer at the EPFL, who is synthesizing analogs of one of our HTS hits (compound 9) for SAR studies. These three additional collaborations add to our ongoing studies and will increase our chances of identifying inhibitors of the IgE:FcR

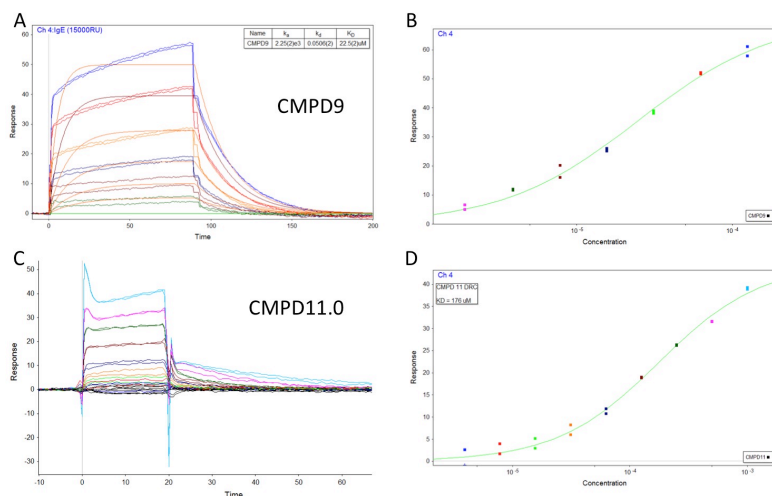


Figure 5 SPR binding analysis of HTS lead compounds 9 and 11.

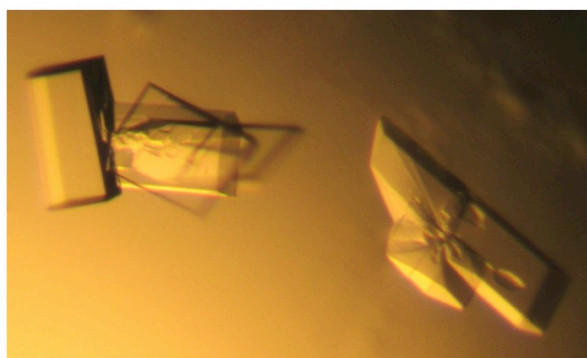


Figure 6. Crystals of IgE-Fc obtained in the presence of compound 9.

variants of this compound in collaboration with the Cramer laboratory at EPFL to test our hypotheses regarding its functional interactions with IgE.

We have also conducted crystal soaking experiments with both of these compounds and collected numerous datasets, but have not yet observed convincing electron density for either of these small molecules. We have recently completed data collection on multiple crystals that were grown in the presence of compound 9 (Figure 6) or compound 11 under new crystallization conditions. The analysis of these data is ongoing. We note that obtaining co-crystal structures of weakly binding ligands is often challenging, but we are continuing to pursue these studies given the high value that structural data would provide on the project. We are also pursuing complexes of analogs that exhibit binding by SPR in parallel with the original compounds. However, successful observation of the small molecule electron density may require some further optimization of compound affinity, as we are pursuing for compound 9 with the Cramer laboratory.

During the past year we purchased a small molecule fragment library consisting of 5000 compounds from Maybridge and Life Chemicals, which was assembled by Bruce Koch at Stanford in consultation with other experts. We have also obtained access to an additional 1000 compound fragment library through the Wakatsuki laboratory in the Department of Structural Biology. While we are planning to use a Biacore T200 SPR instrument (available in the Stanford PAN facility) for screening these libraries, we were able to initiate a screen of

interaction.

Our studies on the top three hits from our HTS screen (compounds 9, 10 and 11) have included further inhibition studies, direct binding studies using SPR and thermofluor assays and crystal soaking and co-crystallization studies for structure determination. We have found that compound 10 obtained from different sources shows variable inhibition in our functional

assay and has not shown promising behavior in direct binding studies. We have therefore focused on studies of compounds 9 and 11. We have observed binding of these two compounds to IgE-Fc in SPR studies (Figure 5) that appears promising. However, we note that the compounds show a slow phase of dissociation in SPR traces, which may indicate non-ideal behavior. We have studied commercially available analogs of these compounds and have produced an initial, simple SAR profile for compound 9. We are in the process of synthesizing

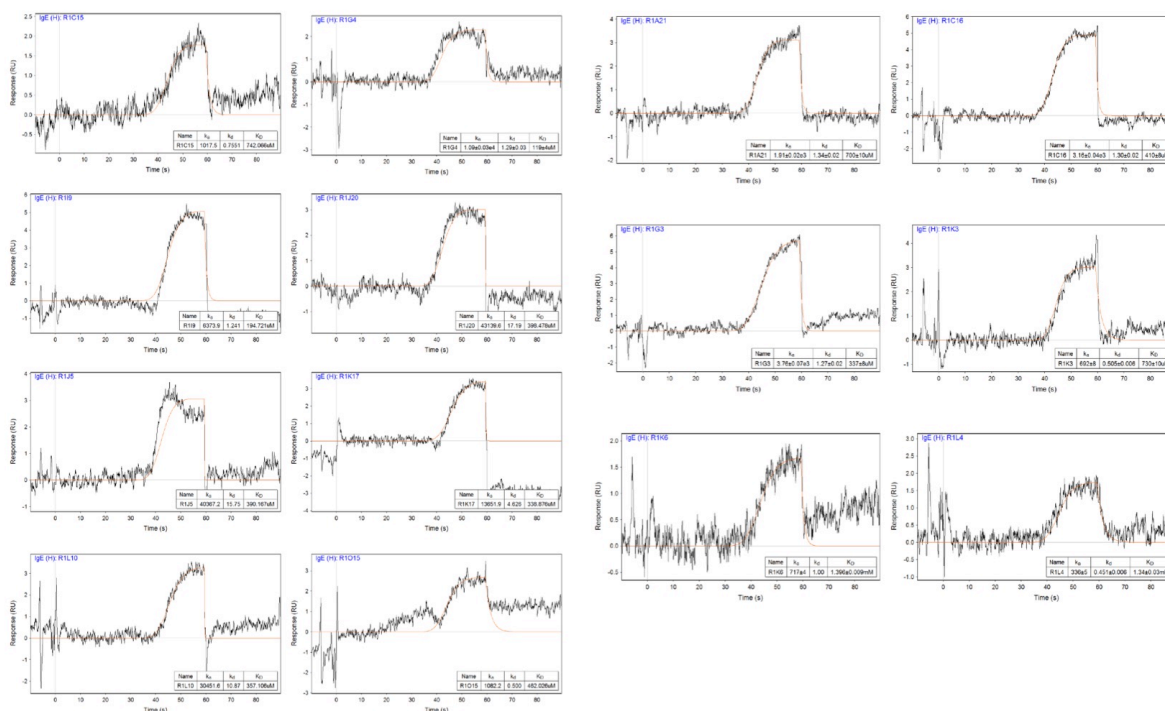


Figure 7. Example data traces for fragment hits from the SensiQ SPR screen with IgE Fc.

a subset of the 5000 compound library using a SensiQ SPR instrument, which carries out a 1 step, concentration gradient screen with high sensitivity comparable to the T200. After optimizing the IgE coupling conditions, we were able to screen 960 compounds out of the 5000 corresponding to two Maybridge plates and 1 Life Chemicals plates. This screen identified ~14 fragment hits with a wide range of estimated K_d values, ranging from ~150 μ M to > 1 mM (Figure 7). This represents a hit rate of ~2%, which is reasonable for low affinity, fragment interactions. Interestingly, some of the fragment hits fall into families of related compounds, providing a potential set of variants for initial SAR analysis

We have followed up on the initial screen by conducting quadruplicate dose-response binding analysis using our Biopix SPR instrument. We have initially analyzed three representative top binding candidates, referred to as TZL1, TZL2 and BZL1. BZL1 showed good dose-

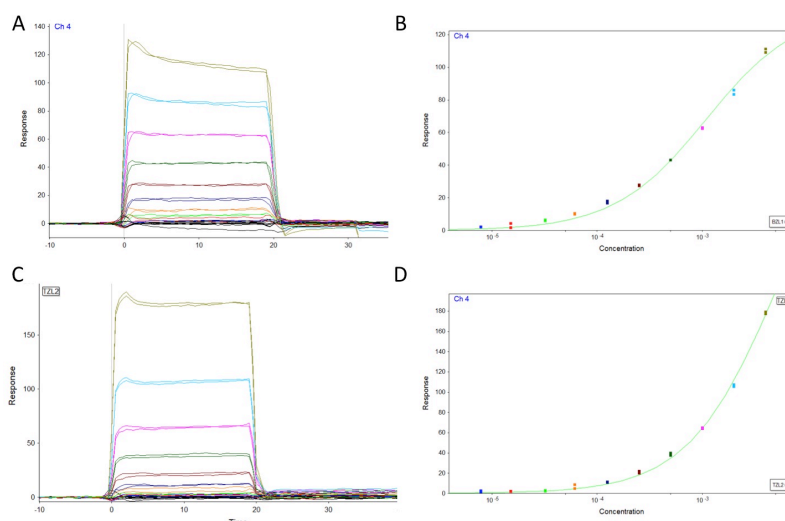


Figure 8. Dose response binding curves for the BZL1 and TZL2 fragments with IgE. Panels A and B show the data and binding curve for the BZL1 fragment with IgE-Fc, respectively. The estimated K_d for this interaction is ~1.1mM. Panels C and D show the data and binding curve for the TZL2 fragment with IgE-Fc, respectively. The estimated K_d for this interaction is ~5 mM.

response binding behavior (Figure 8A,B) with an estimated K_d of ~ 1 mM. TZL1 and TZL2 are closely related compounds, but only TZL2 showed good dose response binding to IgE with an estimated K_d of ~ 5 mM (Figure 8C,D), providing an indication of which functional groups on TZL2 are important for interactions with IgE. We have followed up on these studies by analyzing analogs of these lead fragments that are available commercially and present in our two fragment libraries. We are also pursuing co-crystal structures of these fragments with IgE to further validate their specific binding and to provide a structural basis for selecting further analogs for purchase or synthesis. While the affinity of the fragments is in the millimolar range, this is typical for initial hits in fragment based screening and further modifications can lead to significant improvements in binding affinity. We are excited to continue following up on these initial fragment hits as well as completing our screening of our two fragment libraries in the coming year.

Opportunities for training and professional development. Luke Pennington, a graduate student on the project, and Sarathy Karunan Partha, a research associate, both attended scientific meetings and presented their research results in the past year.

How were the results disseminated to communities of interest. The results from these studies were disseminated by publication (Pennington *et al*, *Nat. commun.*, 2016) and through presentations at conferences. TJ presented lectures based on these studies at two meetings in the past year (IgE Regulation in Allergic Disease Workshop, NIH/NIAID, April, 2016; FASEB meeting IgE and Allergy, 50 Years and Onward, July, 2016). Luke Pennington presented a poster at the FASEB meeting and has given oral presentations at Stanford in the MSTP and Immunology annual retreats. Sarathy Karunan Partha attended the Drug Discovery Chemistry Conference, 2016 and presented a poster on our small molecule screening efforts.

Plans for the next reporting period. As described above, we are continuing with our studies as proposed.

4. IMPACT:

Impact on the principal discipline. Our major public contribution over the past year has been the determination of the omalizumab:IgE structure and development of an omalizumab-resistant IgE for both functional and potential therapeutic applications. These studies have garnered significant interest.

Impact on other disciplines. Nothing to report.

Impact on technology transfer. We patented our omalizumab-resistant IgE construct and are in discussions with a pharmaceutical company that has shown interest in using this technology in the development of IgE-based anti-cancer antibodies.

Impact on society. Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach. Because of our success in developing the yeast display system within the laboratory, we have refocused our studies on using this as the primary platform for the discovery and engineering of disruptive IgE antibodies. This technology gives us much greater control over the process of identifying and modifying anti-IgE antibodies as compared to our original plan of outsourcing antibody production by phage display or by immunization. The development of a

general approach to the identification of antibodies that have disruptive activity would also open up this approach to a broader set of disease targets. For our small molecule studies, we have noted that our HTS leads exhibit non-ideal binding interactions with IgE, and we have expanded our search for lead compounds using a variety of new approaches, including fragment-based and DNA-encoded library screening. We will continue with our original HTS lead compounds but are excited to further develop our additional approaches and follow up on our fragment lead compounds in the coming year.

Anticipated problems or delays. Nothing to report

Changes in human subjects, vertebrate animals, biohazards and/or select agents. Because of our success in selecting novel anti-IgE antibodies using a yeast scFv display library, we are not currently planning to conduct immunization experiments in mice.

6. PRODUCTS:

Publications. Pennington LF, Tarchevskaya S, Brigger D, KC, Eggel A, Jardetzky TS. Structural basis of omalizumab therapy and omalizumab-mediated IgE exchange. Nat Commun. 2016 May 19;7:11610. doi: 10.1038/ncomms11610. PubMed PMID: 27194387.

Website or other internet sites. Nothing to report.

Technologies or techniques. Nothing to report.

Inventions, patent applications and/or licenses.

“OMALIZUMAB RESISTANT IGE VARIANTS AND THEIR USE IN ANTI-IGE THERAPY,” U.S. provisional application serial no. 62/217,709, filed on September 11, 2015

Other products. Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Individuals working on the project.

<i>Name</i>	Theodore Jardetzky
<i>Project role</i>	PI
<i>Researcher Identifier</i>	
<i>Nearest person month worked</i>	1.2 months
<i>Contribution to project</i>	Directed research
<i>Funding support</i>	

<i>Name</i>	Luke Pennington
<i>Project role</i>	Graduate student
<i>Researcher Identifier</i>	
<i>Nearest person month worked</i>	12 months
<i>Contribution to project</i>	Refined structure of the IgE:omalizumab complex; generated bivalent antibody constructs, generated omalizumab-resistant IgE, conducting yeast display experiments
<i>Funding support</i>	Immunology training grant

<i>Name</i>	Svetlana Tarchevskaya
<i>Project role</i>	Research Associate
<i>Researcher Identifier</i>	
<i>Nearest person month worked</i>	12 months
<i>Contribution to project</i>	<i>Crystallized IgE:omalizumab complex, conducted small molecule inhibition experiments, conducting crystallization trials of Fab:IgE complexes</i>
<i>Funding support</i>	
<i>Name</i>	Sarathy Karunan Partha
<i>Project role</i>	Research Associate
<i>Researcher Identifier</i>	
<i>Nearest person month worked</i>	12 months
<i>Contribution to project</i>	Conducting inhibition studies on lead compound analogs, pursuing co-crystal structures of inhibitors with IgE, has designed/obtained peptide-based inhibitors, conducting screening with fragment and combinatorial libraries, developing alternative validation assays for small molecules
<i>Funding support</i>	

Changes in other support.

The following grants have ended:

1. NIH/NIAID R21 AI103722 Jardtetzky, PI 2/13/2014-1/31/2016
“Human Cytomegalovirus Entry Glycoprotein Complexes”; The focus of this proposal is to study CMV gHgL complexes involved in tissue tropism and membrane fusion.
2. NIH/NIAID R56 AI119168 Hsieh, PI 7/1/2015-6/30/2016
“Defining the immunological niche of Schistosoma haematobium IPSE”
The focus of this proposal is to investigate the role of the S. haematobium IPSE protein in infection.
3. NIH/NIGMS R01 GM61050 Jardtetzky (PI) 4/1/2011-3/31/2016
“Structural studies of paramyxovirus fusion proteins”; The specific aims focus on investigation of the HN and F protein structures and their interactions that are important for membrane fusion and viral entry.
4. NIH/NIAID R56 AI 38972 Jardtetzky (PI) 8/1/14-7/31/15
“Structural studies of IgE receptors”; This proposal focuses on understanding DARPin-mediated disassembly of IgE-receptor complexes that are central to most allergic responses.

Other organizations. Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS:

Nothing to report.

9. APPENDICES: n/a